Pharmacovigilance and pharmacogenetic discussions at WorldPharma 2010

Gordon Mallarkey and Arduino A. Mangoni

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The 16th World Congress on Basic and Clinical Pharmacology was held recently in Copenhagen, Denmark. This report summarizes some of the presentations made at focused conference and workshop sessions on pharmacovigilance and pharmacogenetics.

Improvements in surveillance

Professor Sir Alasdair Breckenridge (Medicines and Healthcare Products Regulatory Agency, London, UK) reminded us that pharmacovigilance is all about finding evidence of harm and extending our knowledge of safety. New drugs can receive marketing authorization but will have scant safety data because these are gleaned from a handful of phase III trials that are too small to pick up adverse events and do not represent the eventual ‘real-world’ patients. Further, postmarketing studies are not regulated and most of them are not performed or completed. Passive surveillance, such as spontaneous reporting of adverse events, is the basis of most systems and generates signals (e.g. prescription event monitoring) that can be investigated in large clinical databases. Active surveillance attempts to find safety problems from database studies and random allocation (e.g. clinical trials with safety as a primary endpoint). Actively investigating existing databases carries the risk of finding statistically significant associations by chance alone, for example, a type 1 error where a false-positive result occurs. Professor Breckenridge believes we need to move from reactive to proactive methodology, change from data management to risk management and move up the evidence hierarchy.

The World Health Organization (WHO) and Uppsala Monitoring Centre aim to strengthen national pharmacovigilance systems, and Dr Lembit Rago (WHO, Geneva, Switzerland) reported that there are now 126 participating countries and case reports are processed and maintained at the WHO Collaborating Centre for International Drug Monitoring in Uppsala. Professor Ulf Bergman (Karolinska Institute, Stockholm, Sweden) gave an overview of pharmacovigilance activity in Stockholm. The original intention was to detect new, unexpected, adverse drug reactions (ADRs), so-called type-B reactions, and form sufficient signals to generate hypotheses for confirmation in pharmaco-epidemiological studies. Professor Bergman commented that the majority of ADRs are in fact type-A reactions, that is, they are already documented and may be predicted and prevented. A concerted effort was made to provide feedback of ADRs to the emergency departments of Stockholm hospitals, which involved the introduction of ICD code Y57.9 (unintended use of therapeutic use of drugs) as a quality marker. This marker has improved physicians’ awareness of ADRs; in 2009 there were 500 ADR reports per million inhabitants received. It will be interesting to know if this leads to improved patients’ outcome. The records are analyzed and reports produced to improve prescribing quality.

Professor Joerg Hasford (Ludwig-Maximilians University, Munich, Germany) questioned the need for case-based pharmacovigilance (CBP) now that pharmaco-epidemiological databases (PED) hold formidable amounts of data.

Correspondence to:
**Gordon Mallarkey, PhD,
MRPharms**
Sage Publications Ltd, 1
Oliver’s Yard, 55 City Road,
London EC1Y 1SP, UK
[mallarkey@
sagepub.co.uk](mailto:mallarkey@sagepub.co.uk)

**Arduino A. Mangoni, MD,
PhD, MRCP(UK), FRCP,
FRACP, FESC, FACC**
Chair, Medicine of Old Age,
Division of Applied
Medicine, Section of
Translational Medical
Sciences, School of
Medicine & Dentistry,
University of Aberdeen,
Polwarth Building,
Foresterhill, Aberdeen
AB25 2ZD, UK

CBP includes spontaneous reporting and any monitoring of alleged ADRs. It suffers from under-reporting and poor quality of data as well as confounding because of polypharmacy in patients with comorbid conditions. However, it provides relatively rapid and inexpensive reporting and includes prescription as well as over-the-counter medications for a wide population of patients. On the other hand, PED include prescription drugs only usually from outpatients. It may be harder to access patients' files with PED than CPB and so ascertain a clear picture of cofactors (e.g. smoking, alcohol) and comedications. Thus, Professor Hasford argues that CPB has advantages over PED and may be better from a patient safety point of view. Whilst both approaches have shortcomings and improvements can be made in both cases, it may be practicable to use data from both systems to better inform us about the safer use of medicines. More evidence is required to confirm this in different populations and healthcare systems.

New avenues

The screening of observational healthcare datasets, such as health insurance claims data and electronic medical records (EMRs), is receiving increased attention, said Dr Andrew Bate (Pfizer Inc., New York, NY, USA). Several initiatives are underway for large-scale screening and assessment of observational longitudinal datasets. A variety of methods are being implemented, for example, EMRs of pancreatitis with omeprazole prescribing provided valuable data compared with spontaneous reporting. Evidence is accumulating that surveillance of observational data could show adverse events earlier than current methods, but the challenge is to identify true findings from false positives, and further research is required into how such analyses are further investigated.

Professor Simon Thomas (University of Newcastle, Newcastle, UK) believes that the toxicity of drugs in overdose should be considered by regulatory authorities. For many drugs, acute overdose causes more fatalities than ADRs. Poisoning may be helpful in elucidating dose-related ADRs (e.g. QT prolongation with astemizole). Poisons centers have overdose information that they could provide to complement data from spontaneous reports. Thus, provision of overdose information at an early stage could become part of a pharmacovigilance plan.

Advanced therapies include gene therapy, somatic cell therapy, and tissue engineering products. Dr Brian Edwards (NDA Regulatory Science Ltd, Leatherhead, UK) presented a discussion of the approaches to safety that need to be made for these products.

Pharmacovigilance guidelines have been produced to ensure their safe use and administration. Risk management plans are required involving follow up and quality management, and they need to involve a thorough knowledge of the product, its pharmacokinetic characteristics and how it is stored and administered. Possible adverse reactions are numerous and may include transmission of infectious agents, graft dysfunction/rejection, auto-immunity induction/immunogenic reactions, and possible vector reactivation/integration of genetic material into the host genome. Risk-minimization activities, such as training, communication, and education, also need to be in place, and an understanding of zero tolerance to spillage.

Have we got it right?

Professor Nicholas Moore (University of Bordeaux, Bordeaux, France) presented a lively discussion about the possible failings of ADR monitoring and prevention. About 99% of ADRs that occur in clinical practice are well known and documented, yet patients are still being given these medications. In France, this accounts for more than 3 million GP consultations each year and 140,000 hospital admissions. He argues that drug regulatory authorities and the pharmaceutical industry talk to each other but they do not really interact well with healthcare professionals and patients. He suggests that greater awareness of potential ADRs by doctors and patients would be a positive future initiative. Finally, he said we need to account for unrecognized ADRs such as the falls and deaths that ensue as a result of benzodiazepine therapy. These may be well established among the scientific community but perhaps are less well known in primary care.

Professor Dr Petra Thurmann (University Witten/Herdecke, Wuppertal, Germany) gave a thought-provoking presentation on measures to improve drug safety and prevent adverse drug events (ADEs). She said that there has been no decrease in the number of ADEs over the last 20 years. Further, the evidence shows that a considerable number of ADEs are preventable in

community and hospital settings. The scenario that occurs with about 10% of drugs is that a 'Dear Doctor' letter needs to be issued at some point. Frequent labeling changes may also be required and can lead to 'black box' warnings, which may not be effective. For example, cisapride was eventually withdrawn after three black box warnings failed. About 29% of launched drugs are eventually withdrawn. Most cases of ADRs are physician provoked. It is not clear if physicians had all of the details available at the time of prescription. Lists of drugs commonly known to cause ADRs and ADEs are well published and distributed and even incorporated into computer-assisted prescribing tools. However, this has not been proven unequivocally to show any benefit. Professor Thurman said that we need to ensure clinical pharmacists form part of the team as their involvement in medicines management has been shown to reduce ADRs. Further strategies include re-evaluating regulator actions aimed at risk reduction, and increasing physicians' knowledge of the general principles of clinical pharmacology and drug prescribing.

Improving medicines safety and pharmacovigilance in Africa

There has been huge growth in pharmacovigilance activity in Africa in the last 10 years, and it will continue to develop and improve with ongoing support from WHO and others, said Professor Ambrose Isah (University of Benin, Benin City, Nigeria). More and more medicines have become available in Africa and this has been accompanied by challenges to drug safety. Regulatory systems need improvement as well as public health programs specific to the drugs and diseases in Africa. Irrational use of medicines and the preponderance of counterfeit medicines are common in Africa. Emphasis has been placed on increasing the reporting of ADRs; however, there are many more steps to implement.

Dr Alex Dodoo (University of Ghana Medical School, Accra, Ghana) stated that pharmacovigilance systems are essential in Africa; however, they need to be robust so that the cost of instituting them is repaid by meaningful results such as improvements in identifying adverse events, preventing known ADRs and maximizing the rational use of medicines so that benefits are seen by patients and the health system. The 'yellow card' system is essential to spontaneous reporting but it suffers from severe under-reporting even in developed countries. Thus, any

pharmacovigilance system must be designed and instituted so that it is not frivolous and can help to solve imminent national issues, such as monitoring the introduction of new drugs for HIV/AIDS and tuberculosis. Many more examples exist in Africa where real-life safety data on new medicines are urgently required.

Dr Dodoo gave a further presentation entitled 'Between a rock and a hard place – safety monitoring of medicines for neglected diseases'. The 'rock' he explained was the vast range of neglected diseases that afflict millions of poor people in developing countries. He vividly described the challenges encountered in dealing with diseases such as tuberculosis, leishmaniasis, trachoma, schistosomiasis, Chagas' disease, African trypanosomiasis, and others. The 'hard place' describes the range of medicines used to manage these diseases, which are mainly old, of low efficacy and usually toxic (e.g. praziquantel, niclosamide, ivermectin, amphotericin B, etc.). Infected patients have no option but to be treated with these drugs because of the extreme disease course. This inevitably forces them to deal with the adverse effects of the drugs. Currently there is no incentive for pharmaceutical companies to develop new and safer medicines to poor populations. So, what is the middle ground? Dr Dodoo emphasized that safety monitoring is essential so that we know the nature and incidence of adverse events, can identify risk factors, and develop strategies to minimize harm. WHO has said that expanding preventive chemotherapy will likely lead to more adverse events and ADRs, thus, newer and safer drugs are required. Governments in each country need to look after their population and attempt to encourage development of new drugs for neglected diseases that are more effective, safe and affordable.

Pharmacogenetic advances and hurdles

Drug-induced liver injury (DILI) is a rare but serious event seen in 1 in 10,000 to 1 in 100,000 patients. Professor Ann Daly (Newcastle University, Newcastle, UK) gave a presentation on recent genetic advances that have extended our knowledge of DILI. It may be due to a rare genetic variant, interaction between several more common variants or a gene–environment interaction. Identification of DILI requires a large number of patients because of their rarity, and a clear phenotype is crucial. The mechanism appears to involve a reactive intermediate that binds to proteins producing

direct damage or an inappropriate immune response. Drugs involved may be subject to considerable metabolism (e.g. isoniazid and diclofenac), some metabolism (e.g. flucloxacillin, metabolism plus immune-related DILI), and drugs with no clear metabolism (e.g. clavulanic acid, immune-related DILI). The human leukocyte antigen (HLA) associations of several drugs are now known, for example, flucloxacillin DILI is associated with class I HLA allele B*5701.

Professor Simon Mallal (Royal Perth Hospital and Murdoch University, Perth, WA, Australia) believes we need to keep working to move pharmacogenetic tests from bench to practice as most are being 'lost in translation'. He described how HLA-B*5701 screening for potential abacavir hypersensitivity has become an accepted pharmacogenetic test in the developed world (this resulting from Professor Mallal's breakthrough research in 2002). He then reviewed the potential for other tests that might screen patients for potentially life-threatening, drug-induced hypersensitivity reactions and severe cutaneous ADRs. The HLA-B*1502 allele has been identified in carbamazepine-induced hypersensitivity in Asian populations. There appears to be two alleles involved in nevirapine-induced

hypersensitivity with differing immunopathogenesis; thus, it may be too difficult to get a successful test into the clinic. There are many hurdles to contend with involving specificity and cost. If a single allele is known to produce a highly specific hypersensitivity then there is a good chance that it could become a cost-effective screening test. Several alleles and lower specificity are less likely to produce a practical test.

Professor Andrew Somogyi (University of Adelaide, Adelaide, SA, Australia) commented that pharmacogenetic testing in Australia is stuck because it is regarded as a pathology service. Most persons cannot afford to pay for testing so it needs the government to decide to subsidize it. Such applications are complicated and time consuming. Once a test is approved, there needs to be an infrastructure in place including guidelines so that results are interpreted correctly. Pathology services also need to agree to take on the testing and health professionals need to be trained. Professor Somogyi said that the response from government to a report in 2008 and a summit last year are still awaited. It appears to be a slow and frustrating process.

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